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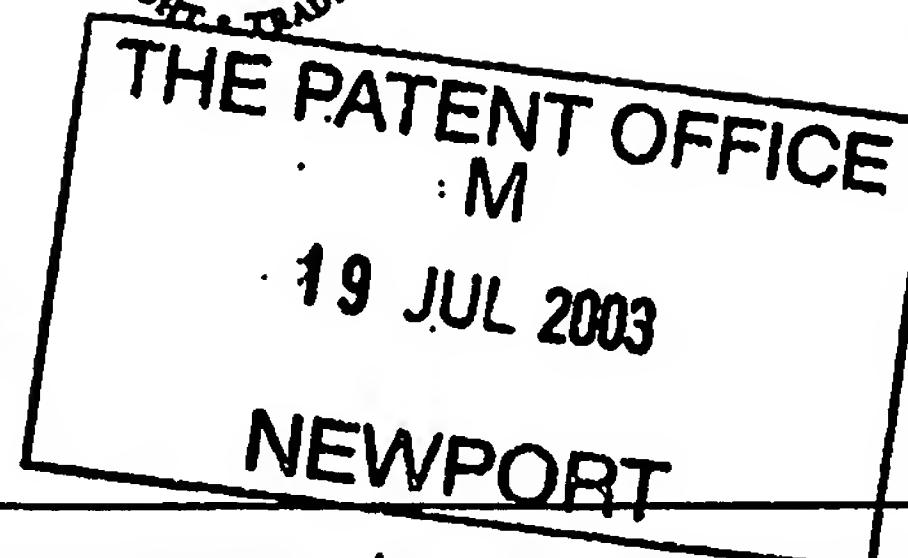
Andrew Gersley
19 August 2004



1777

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



The Patent Office
Cardiff Road
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South Wales
NP10 8QQ

1. Your reference

100182676GB.

2. Patent application number

(The Patent Office will fill in this part)

0317192.3

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Smith & Nephew, plc
15 Adam Street
LONDON WC2N 6LA

Patents ADP number (if you know it)

03969284001

03969284001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

High Strength Bioresorbable Co-Polymers

5. Name of your agent (if you have one)

John Hobbs

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Smith & Nephew plc
Group Research Centre
York Science Park
Heslington
York YO10 5DF
United Kingdom

Patents ADP number (if you know it)

07260854001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

YES

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

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Patents Form 1/77

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Continuation sheets of this form

Description

6 / W-

Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Date 18/07/03

JOHN HOBBS

John Hobbs 01904 824050

12. Name and daytime telephone number of person to contact in the United Kingdom

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HIGH STRENGTH BIORESORBABLE CO-POLYMERS

The present invention relates to polymer compositions and artefacts made therefrom. In particular the present invention relates to polymers having high 5 mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body. More particularly the invention relates to bioresorbable glycolic acid-containing co-polymers and to implantable medical devices made therefrom.

Polymer compositions comprising poly-glycolic acid (PGA) and glycolic acid-10 containing co-polymers have an established use for medical implants. It has also been proposed that certain mechanical properties may be improved by extruding PGA melts or by drawing PGA in a plastic state. Isotropic PGA has a tensile strength of between 50 to 100 MPa and a tensile modulus of between 2 and 4 GPa. A commercial product (SR-PGA) comprising PGA 15 fibres in a PGA matrix has a flex strength and modulus of 200 – 250 MPa and 12 – 15 GPa, respectively. It is also reported in the literature that melt spun PGAs have tensile strength of about 750 MPa and a modulus from 15 to 20 GPa. In US Patent No. 4968317 an example of a drawn PGA is stated to have a tensile strength of about 600MPa.

20 Although PGAs having improved strength characteristics are known, none of the known materials have the mechanical properties approaching those of the metals conventionally used for load bearing implantable medical devices. A commercial alloy used for orthopaedic implant devices, known as Ti-6-4, comprises titanium with 6% aluminium and 4% vanadium and has a tensile 25 strength in the range of 800 to 1000MPa and a modulus in the order of 100GPa.

One possible reason that PGA and glycolic acid-containing co-polymers cannot currently be processed to achieve the desired strength of metals is that when the polymers are processed by common methods to produce orientated 30 fibres (e.g. stretching the material at a constant rate in a heated chamber or

tank) additional polymer crystallisation occurs during the process. The crystals in the polymer act such that they prevent further polymer orientation. This crystallisation of the polymer limits the mechanical properties that can be achieved by drawing glycolic acid-containing co-polymers to around 800MPa, as described in the prior art.

5

We have found that polymer compositions comprising glycolic acid-based co-polymers may be processed such that the resultant composition has significantly greater strength, typically of the order of greater than 1200MPa with a commensurate increase in modulus, typically in excess of 22 GPa.

10 In accordance with the present invention there is provided a polymer composition comprising glycolic acid as a co-polymer with at least one other bioresorbable monomer, or a functional derivative of said co-polymer, having a tensile strength of at least 1200MPa.

15 The polymer composition gains this level of tensile strength by means of a novel processing method that results in an orientated structure, for example an orientated fibre.

The present invention further provides an artefact comprising a polymer composition including glycolic acid or a functional derivative thereof having a tensile strength of at least 1200MPa.

20 ~~The polymer composition may be comprised entirely of glycolic acid-based co-polymer or a derivative thereof, or may comprise a glycolic acid-based co-polymer-containing blend with other polymers. Preferably the polymer composition is entirely glycolic acid-based co-polymer.~~

25 Similarly, artefacts formed from the polymer compositions of the invention may consist wholly of the polymer compositions of the invention or may be composites consisting only partially of the polymer compositions of the invention.

Aptly the artefact contains 10 to 80% by volume of the polymer compositions of the invention, suitably the artefact contains up to 60% by volume of the

polymer compositions of the invention, preferably the artefact contains at least 40% by volume of the polymer compositions of the invention and typically the artefact contains approximately 50% by volume of the polymer compositions of the invention.

5 We have found that in order to achieve the high strength exhibited by the compositions of the invention it is necessary that the glycolic acid-containing co-polymer be rendered into an amorphous state and then immediately drawn to form a highly orientated structure.

This can be achieved by first processing isotropic glycolic acid-based co-polymer granules to form fibres or filaments, thereafter passing the fibres into a quenching bath to form an amorphous structure. Polymer compositions of the present invention may then be produced by drawing the quenched, amorphous glycolic acid-based co-polymer. Preferably this is a drawing process which minimises the time polymer is exposed to elevated temperatures, thus minimising the time for the polymer to crystallise.

In accordance with another aspect of the invention there is provided a process for the manufacture of glycolic acid-based co-polymer compositions comprising increasing polymer chain orientation of a substantially amorphous polymer by drawing at localized points within the mass.

20 Suitably this comprises the steps of forming glycolic acid-based co-polymer or a functional derivative thereof into fibres, for example by melt extrusion or solution spinning; quenching the fibres then subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.

25 Aptly fibres of amorphous glycolic acid-based co-polymer-containing polymers may be prepared by solution spinning or melt extruding the polymer through a die; the filament is then rapidly chilled to produce a substantially amorphous material. Typical chilling methods include blowing a cold gas onto the filament

as it is produced or by passing the filament through a bath of a suitable cold liquid, e.g. water, silicone oil.

A suitable drawing method is zone heating. In this process a localised heater is moved along a length of fibre which is held under constant tension. This process is used in the zone-drawing process as described by Fakirov in Oriented Polymer Materials, S Fakirov, published by Hüthig & Wepf Verlag, Hüthig GmbH. In order to carry out this zone heating fibre can be passed through a brass cylinder. A small part of the cylinder inner wall is closer to the fibre, this small region locally heats the fibre, compared to the rest of the brass cylinder, localising the drawing of the fibre to this location, see figure 1. A band heater can be placed around the brass cylinder to allow it to be heated above room temperature. This heated brass cylinder can then be attached to the moving cross-head of a tensile testing machine and the fibre to be drawn suspended from a beam attached to the top of the testing machine. To draw the fibre a weight can be attached to the lower end of the fibre, the brass cylinder heated to the desired temperature and the cross-head moved to the lower end of the fibre, see figure 2. The polymer draws where the fibre is closest to the brass cylinder, as the cross-head is moved up the length of the fibre, then a length of the fibre can be drawn.

Suitably the fibre can be held taut using a small stress, which is typically below the yield point of the material at ambient temperatures. The fibre can then be heated locally to a temperature which is above the softening point (T_g) but below the melting point such that localised drawing of the polymer occurs, the whole fibre can be treated by movement of either or both the fibre and heated zone such that the full length of the fibre is drawn. This first drawing of the polymer may produce a polymer with improved molecular alignment and therefore strength and modulus. In this first step the conditions are selected such that the material does not substantially crystallise during the process, this requires that either the temperature of the polymer is below the temperature at which crystallisation occurs, T_c , or if the polymer is above T_c the speed at which the heated zone moves along the fibres is fast enough such that the polymer cools below T_c before it has time to crystallise. Further

improvements can be made by subsequent treatments, where the stress applied to the fibre or the zone temperature is increased or both. Both the strength of the fibre and the softening point increase as the degree of molecular alignment improves. The process can be repeated many times, until 5 the desired properties are reached. A final annealing step can be carried out in which the material crystallises under tension in the process; this can further improve the mechanical properties and improve the thermal stability of the final fibre.

In an embodiment of this aspect of the invention there is provided an artefact 10 comprising a poly-glycolic acid in accordance with the invention. For example, the glycolic acid-containing co-polymer fibres can be mixed with other components to form the artefacts. These other components may be polymers, bioresorbable polymers, non-polymeric materials or combinations thereof.

15 Aptly the bioresorbable polymer comprises a poly-hydroxy acid, a poly-caprolactone, a polyacetal, a poly-anhydride or mixture thereof; the polymer comprises poly-propylene, poly-ethylene, poly-methyl methacrylate, epoxy resin or mixtures thereof whilst the non-polymeric component comprises a ceramic, hydroxyapatite, tricalcium phosphate, a bioactive factor or 20 combinations thereof.

Suitably the bioactive factor comprises a natural or engineered protein, a ribonucleic acid, a deoxyribonucleic acid, a growth factor, a cytokine, an angiogenic factor or an antibody.

Artefacts according to the present invention can aptly be manufactured by 25 placing appropriate lengths of strengthened glycolic acid-containing co-polymer fibre into moulds, adding the other components then compression moulding. Alternatively, the strengthened fibres can be pre-mixed with the other components then compression moulded.

In an alternative processing method, artefacts according to the present 30 invention can be manufactured by forming a polymeric component in the

presence of the strengthened fibres by in situ curing of monomers or other precursors for said polymeric component.

Preferably the monomers used in this process do not liberate any by-products on polymerisation as these can compromise the properties of the artefact.

- 5 Aptly at least one of the monomers used in said in situ curing process is a ring-opening monomer that opens to form a poly-hydroxy acid. Typically at least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or a mixture thereof.

The polymer compositions of the invention are useful for the production of

- 10 medical devices, particularly implantable devices where it is desirable or necessary that the implant is resorbed by the body. Thus, artefacts in accordance with the present invention include sutures; tissue-engineering scaffolds or scaffolds for implantation; orthopaedic implants; reinforcing agents for long fibre composites used in resorbable load bearing orthopaedic
- 15 implants; complex shaped devices, for example formed by injection moulding or extruding composites formed by mixing short lengths of chopped fibres with poly-lactic acid; or bone fixation devices, for example formed from relatively large diameter rods (e.g., greater than 1mm) of the compositions of the invention.

- 20 The invention will now be illustrated by the following example.

Example 1

PGA:PLA co-polymer (98% PGA, 2% PLA) was extruded into a water bath to produce a translucent fibre of approx 0.5mm diameter. This fibre was then suspended vertically and a weight of 200g was applied. A heated cylinder of brass with a hole of approx 15mm apart from a small section with a 2mm diameter hole, through which the PGA fibre passes, was heated to a temperature of 90°C and moved along the fibre at a speed of 200 mm/min. The fibre produced was found to have a strength of greater than 1200 MPa and a modulus of greater than 20 GPa.

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